Azacitidine, Venetoclax, and Revumenib for Newly Diagnosed Older Adults with AML with *NPM1*-mutation or *KMT2A*-rearrangement: Updated Results from the Beat AML Consortium

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Joshua F. Zeidner[1], Rina Li Welkie[2], Tara L. Lin[3], Emily Curran[4], Kristin Koenig[2], Wendy Stock[5], Olatoyosi Odenike[5], Yazan F. Madanat[6], Ronan Swords[7], Maria R. Baer[8], William Blum[9], Eytan Stein[10], Rebecca L. Olin[11], Gary Schiller[12], Mona Stefanos[2], Molly Martycz[2], Ying Huang[2], Len Rosenberg[13], Sonja Marcus[13], Timothy L. Chen[2], Ashley O. Yocum[13], Uma Borate[2], John C. Byrd[4], Brian J. Druker[7], Ross L. Levine[10], and Alice S. Mims[2]

1 Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA; 2 The Ohio State University, Columbus, OH, USA; 3 University of Kansas Medical Center, Kansas City, KS, USA; 4 University of Cincinnati, Cincinnati, OH, USA; 5 University of Chicago Comprehensive Cancer Center, Chicago, IL, USA; 6 University of Texas Southwestern Medical Center, Dallas, TX, USA; 7 Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA; 8 University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA; 9 Winship Cancer Institute of Emory University, Atlanta, GA, USA; 10 Memorial Sloan Kettering Cancer Center, New York City, NY, USA; 11 University of California San Francisco, San Francisco, CA, USA; 12 David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA, USA; 13 The Leukemia & Lymphoma Society, Rye Brook, NY, USA

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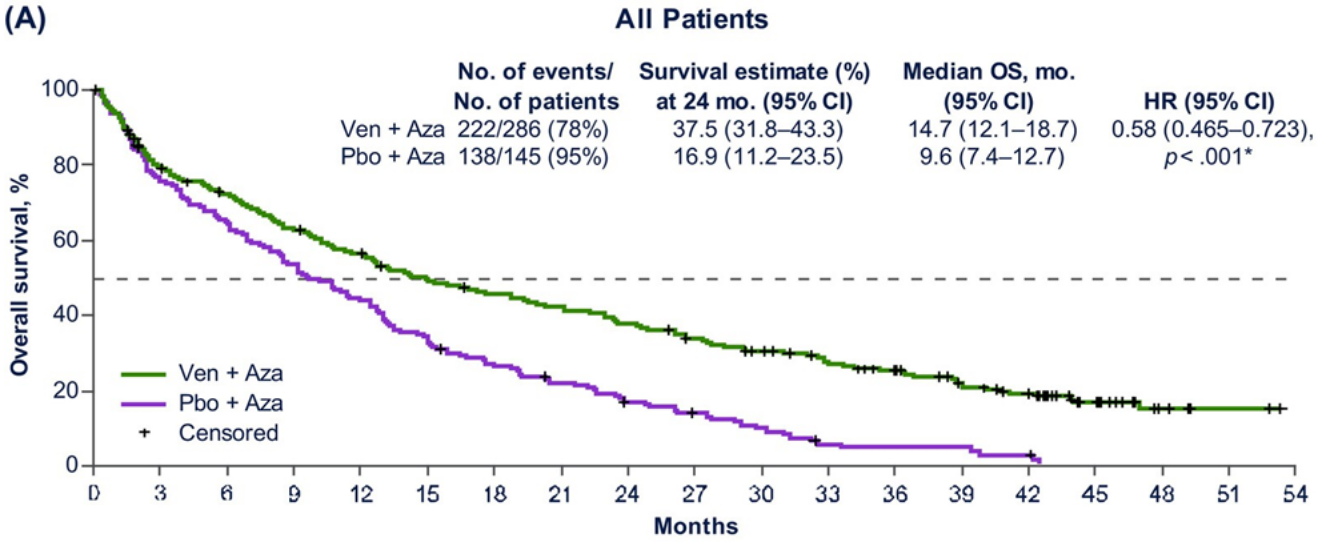
Azacitidine/Venetoclax (Aza/Ven) for Newly Dx Older/Unfit AML

- **VIALE-A: Randomized Phase 3 study of Azacitidine + Venetoclax vs. Azacitidine + Placebo**
- Eligibility: Newly Dx AML ≥75 years or unfit for intensive chemo (Median Age = 76 years)



CR/CRi rates: 67% vs. 29% (p<0.001)

Paradigm shift in management of older adults with AML

- **Long-term outcomes remain poor- 2 year OS <40%**
- **Full CR rates are low (37%) and ~1/3 of pts will not respond to treatment**
- **Dismal outcomes in *KMT2Ar***
  - **Mayo Clinic Analysis: CR/CRi rates = 43%, median OS = 2.5 months in *KMT2Ar* Tx with Aza/Ven**
- **~50% of *NPM1m* AML have Intermediate-risk ELN-2024 (*FLT3-ITD*, *NRAS* or *KRAS* mut)**
  - **Poor outcomes (CR/CRi = 57%, median OS <10 months)**

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DiNardo, *N Engl J Med* 2020; Pratz, *Am J Hematol* 2024; Gangat, *Am J Hematol* 2024, Dohner, *Blood* 2024

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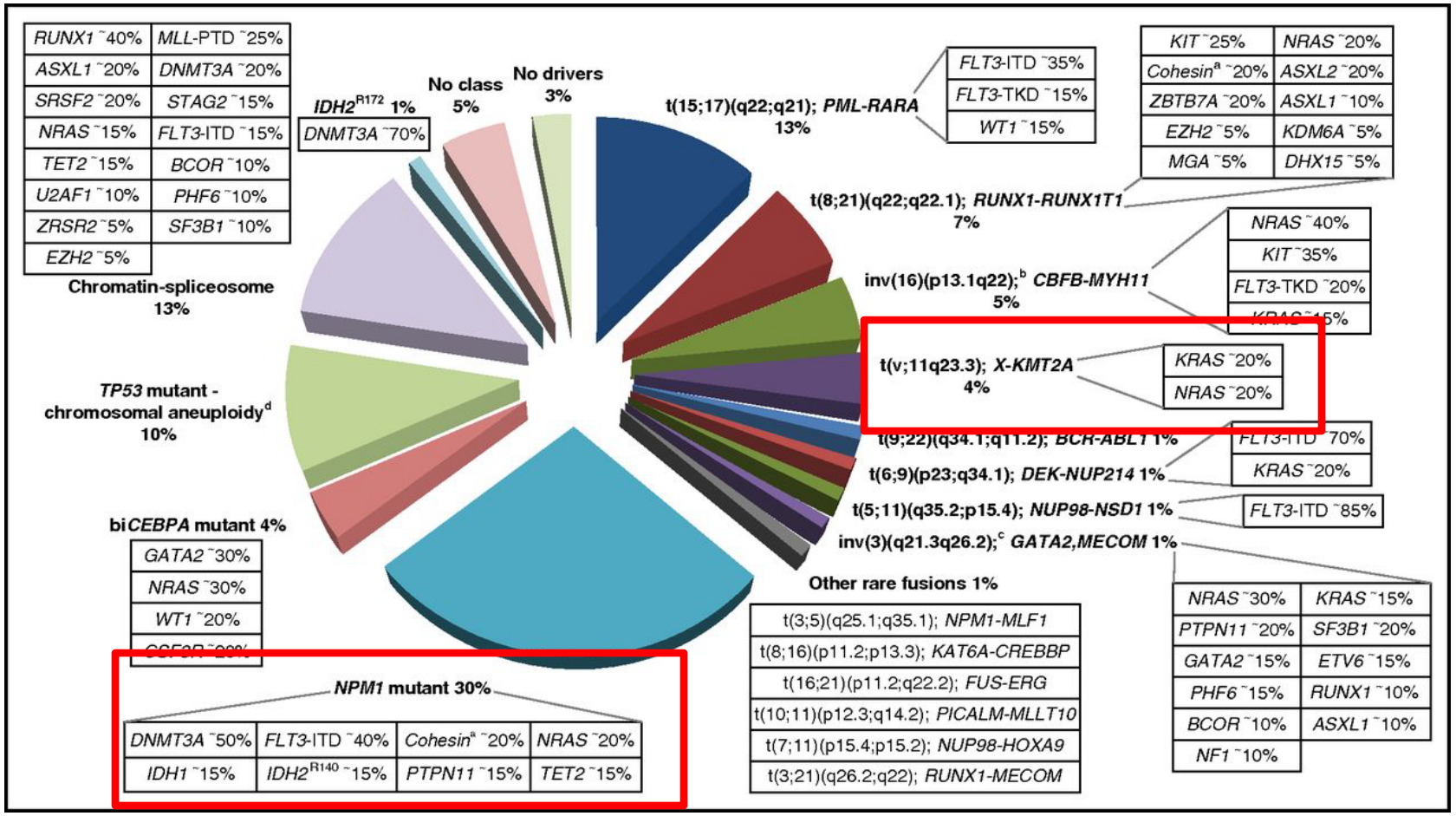
Menin Inhibitors- New Class of Targeted Treatments for *NPM1m* and *KMT2Ar* AML

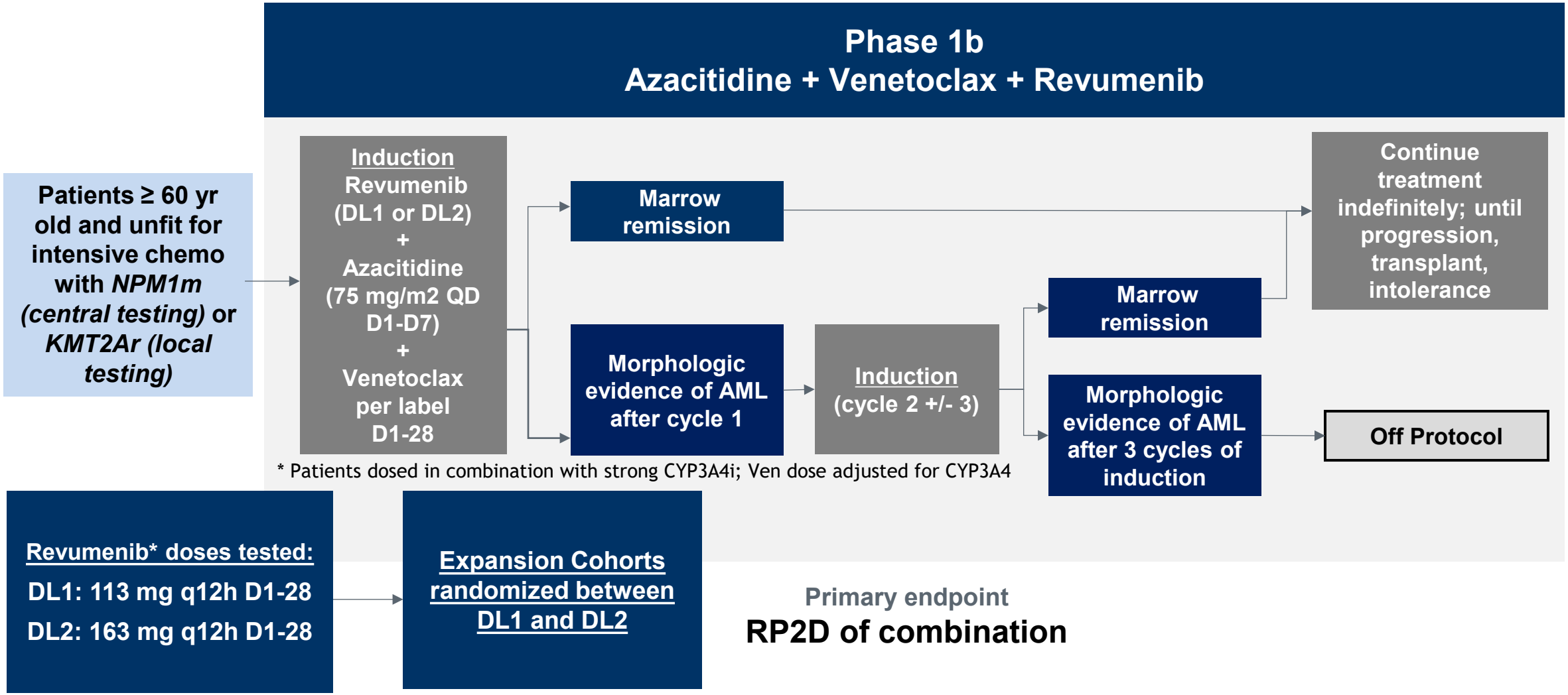


Menin Inhibitors

Revumenib is a first-in-class menin inhibitor approved for R/R acute leukemia with *KMT2A translocation*

Dohner, *Blood* 2017

Beat AML Study Design- Phase 1b Study of Aza/Ven + Revumenib in Newly Dx AML



DL = Dose Level

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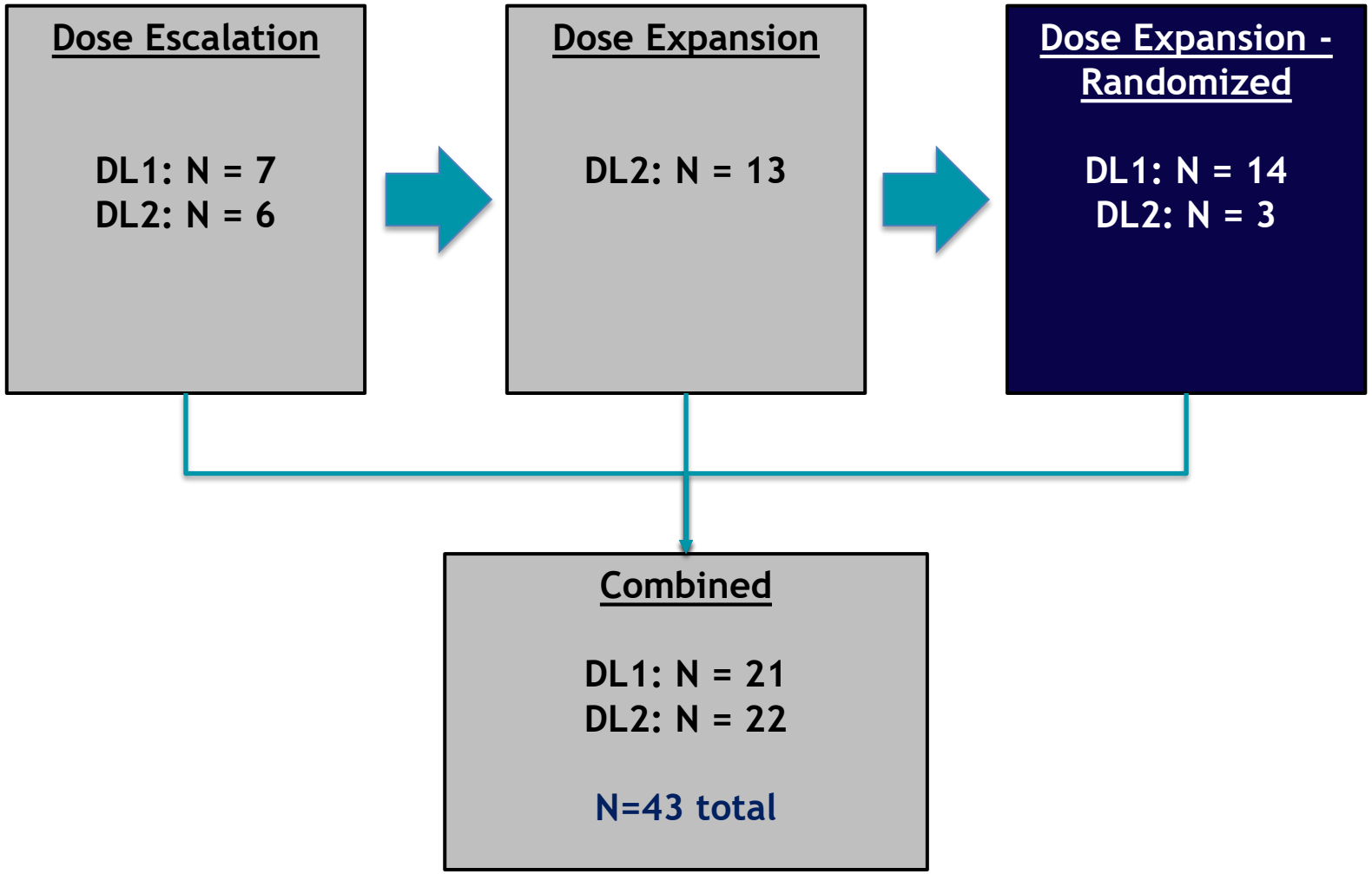
Aza/Ven/Revumenib Enrollment



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Baseline Characteristics of Aza/Ven/Revumenib

Characteristic	DL1	DL2	All		
	(n=21)	(n=22)	*KMT2Ar* (n=9)	*NPM1m* (n=34)	All (n=43)
Age, years, Median (range)	74 (61, 92)	69.5 (60, 84)	67 (60, 81)	73.5 (61, 92)	70 (60, 92)
Age ≥ 75 years, no. (%)	10 (47.6)	7 (31.8)	1 (11.1)	16 (47.1)	17 (39.5)
Gender, no. (%)					
Female	15 (71.4)	8 (36.4)	4 (44.4)	19 (55.9)	23 (53.5)
ECOG Performance Status, no. (%)					
0-1	15 (71.4)	15 (68.1)	8 (88.9)	22 (64.7)	30 (69.8)
2	6 (28.6)	7 (31.8)	1 (11.1)	12 (35.3)	13 (30.2)
WBC, 103/uL, Median (range)	5.0 (0.7, 18.8)	2.4 (1.0, 14.3)	5.0 (1.2, 14.3)	3.2 (0.7, 18.8)	3.2 (0.7, 18.8)
BM Blast (%), Median (range)	63 (15, 94)	60 (16, 95)	78 (55, 84)	54 (15, 95)	60 (15, 95)
ELN 2024 Risk, no. (%)					
Favorable	9 (42.9)	13 (59.1)	5 (55.6)	17 (50.0)	22 (51.2)
Intermediate	11 (52.4)	9 (40.9)	3 (33.3)	17 (50.0)	20 (46.5)
Adverse	1 (4.8)	0 (0.0)	1 (11.1)	0 (0.0)	1 (2.3)
NRAS Mutation, no. (%)					
Present	5 (23.8)	4 (19.0)	3 (33.3)	6 (18.2)	9 (21.4)
KRAS Mutation, no. (%)					
Present	3 (14.3)	2 (9.5)	2 (22.2)	3 (9.1)	5 (11.9)
FLT3-ITD Mutation, no. (%)					
Present	6 (28.6)	5 (22.7)	0 (0.0)	11 (32.4)	11 (25.6)

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Safety and AEs of Aza/Ven/Revumenib

- 1 Hematologic DLT seen in DL1 during dose-escalation
  - No other Heme or Non-Heme DLTs
  - No MTD identified

Grade ≥3 Non-Heme TEAEs

Adverse Event, No. (%)	DL1 (n=21)	DL2 (n=22)	All (n=43)
Febrile neutropenia	5 (24)	6 (27)	11 (26)
Acute kidney injury	4 (19)	4 (18)	8 (19)
Dyspnoea	4 (19)	2 (9)	6 (14)
QTcF Prolongation	2 (10)	3 (14)	5 (12)
Hypokalaemia	1 (5)	4 (18)	5 (12)
Muscular weakness	2 (10)	3 (14)	5 (12)

- Most common Grade 1-2 TEAEs:
  - Nausea (60%), Constipation (53%), QTcF prolongation (44%)

- 30-day & 60-day mortality = 7% (3/43)

Differentiation Syndrome	DL1 N=21	DL2 N=22	All N=43
No. of Patients, (%)	6 (28.6%)	2 (9.1%)	8 (18.6%)
Grade ≥3, (%)	2 (9.5%)	0	2 (4.7%)
Median Time To DS, Days	8	4.5	4.5
DS Duration, Days (range)	5 (2-8)	4 (2-6)	5 (2-8)
Dose Reductions	0	0	0
Dose Interruptions	2	0	2

QTcF Prolongation	DL1 N=21	DL2 N=22	All N=43
No. of Patients, (%)	7 (33.3%)	12 (54.5%)	19 (44.2%)
Grade ≥3, (%)	2 (9.5%)	3 (13.6%)	5 (11.6%)
Median Time To QT, Days	30.5	32	31.5
QT Duration, Days (range)	7.5 (1-133)	8 (0-98)	8 (0-133)
Dose Reductions	1	0	1
Dose Interruptions	4	4	8

- No G4 DS or QTcF Prolongation
- No pt discontinued Revumenib due to DS or QTcF Prolongation

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Treatment Cycle Durations of Aza/Ven/Revumenib

Induction Treatment Cycle Lengths[1]	DL1 N=21	DL2 N=22	All N=43
Median Days, (Range)	41 (28-55)	35 (28-42)	38.5 (28-55)

Continuation Phase Cycles[2] - Median Duration = 42 days		
Delay (weeks)	# of Continuation Cycles	Proportion of All Continuation Cycles
No Delay	13	13%
<1 week	22	22%
1-2 weeks	19	19%
2+ weeks	46	46%

- Overall median duration of induction-phase and continuation-phase cycles similar to Aza/Ven on VIALE-A
- ANC $\geq 0.5 \times 10^9$/L & platelets $\geq 50 \times 10^9$/L prior to each cycle

- **Revumenib dose-reduced first for G4 neutropenia or thrombocytopenia lasting >14 days end of cycle**
  - **Reduced to 21 days every cycle (n=10)**
- Ven dose-reduced at 2nd occurrence- 21 days every cycle
  - **N=7 (22% in continuation phase)**
- No difference between DL1 and DL2 for duration of Continuation Phase Cycles
  - **Median duration of DL1 and DL2 = 42 days**

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1- Time from initiation of induction-phase to initiation of continuation-phase: only includes pts who completed induction-phase and began continuation-phase

2- Continuation Phase cycles only include completed cycles of continuation-phase. Ongoing cycles not included.

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Clinical Outcomes of Aza/Ven/Revumenib

Clinical Outcomes	DL1	DL2	All		
	(n=21)	(n=22)	*KMT2Ar* (n=9)	*NPM1m* (n=34)	All (n=43)
Best Response, no. (%)					
CR	13 (61.9)	16 (72.7)	7 (77.8)	22 (64.7)	29 (67.4)
CRh	0 (0.0)	1 (4.5)	0 (0.0)	1 (2.9)	1 (2.3)
CRi	4 (19.0)	1 (4.5)	1 (11.1)	4 (11.8)	5 (11.6)
MLFS	2 (9.5)	1 (4.5)	1 (11.1)	2 (5.9)	3 (7.0)
Not Evaluable[1]	2 (9.5)	3 (13.6)	0 (0.0)	5 (14.7)	5 (11.6)
ORR (CR/CRh/CRi/MLFS)	19 (90.5%)	19 (86.4%)	9 (100%)	29 (85.3%)	38 (88.4%)
CRc (CR/CRh/CRi)	17 (81.0%)	18 (81.8%)	8 (88.9%)	27 (79.4%)	35 (81.4%)

- **No patient had refractory disease after 1-2 cycles**
- **84% of evaluable patients achieved remission within 1st cycle of therapy**
- **100% of evaluable pts achieved flow MRD-negative remission (sensitivity 0.02%)**
  - **76% after cycle 1; 89% after cycle 2**
- **31% achieved *NPM1m* NGS-negative remission (sensitivity 0.005%)**
- **39% (5/13 pts tested) were *NPM1m* MRD-negative after cycle 2**

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1 Not Evaluable = 5 pts had either early death (n=3) or withdrew from study (n=2) prior to end of cycle 1 BM Bx

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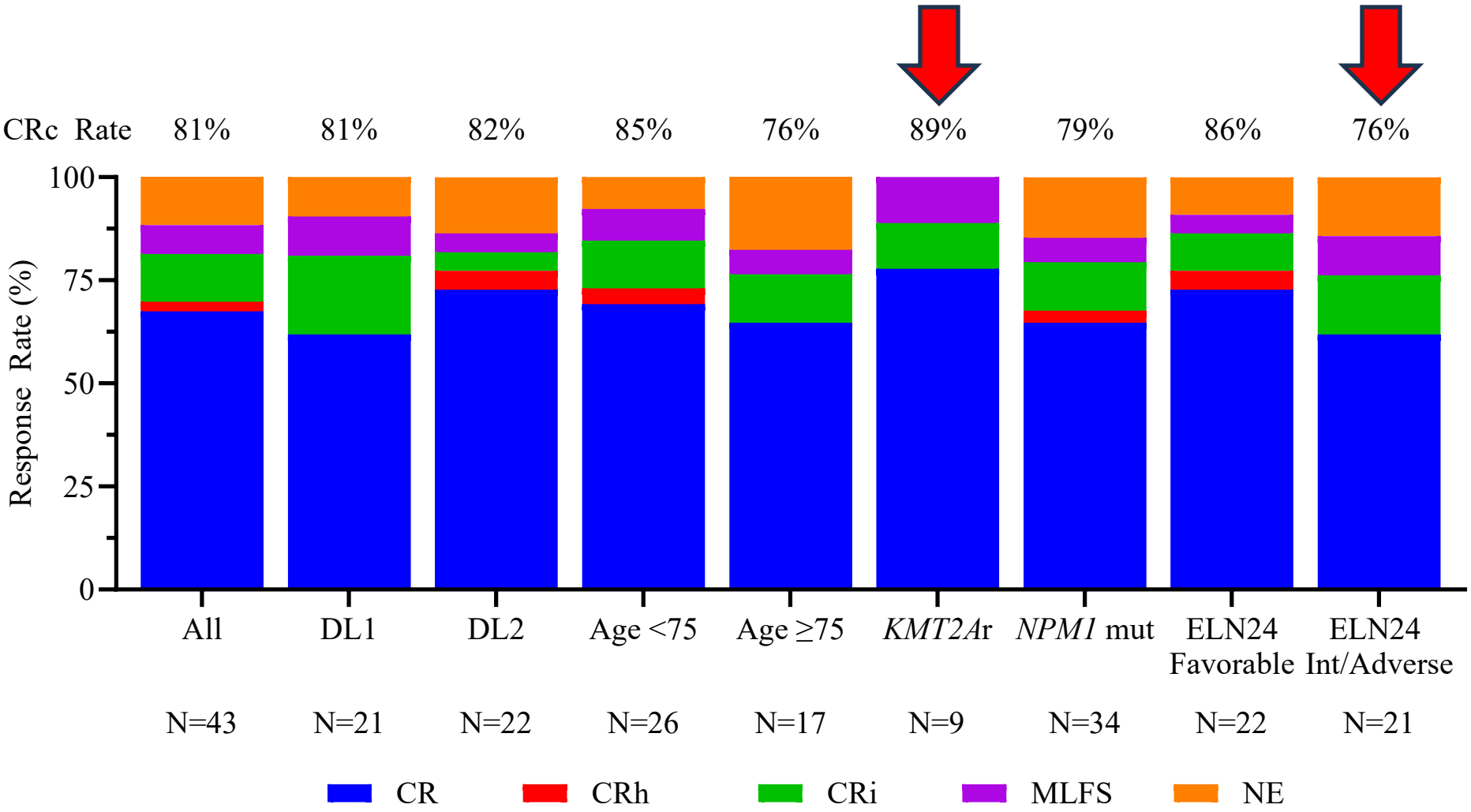
Subset Analyses of Aza/Ven/Revumenib



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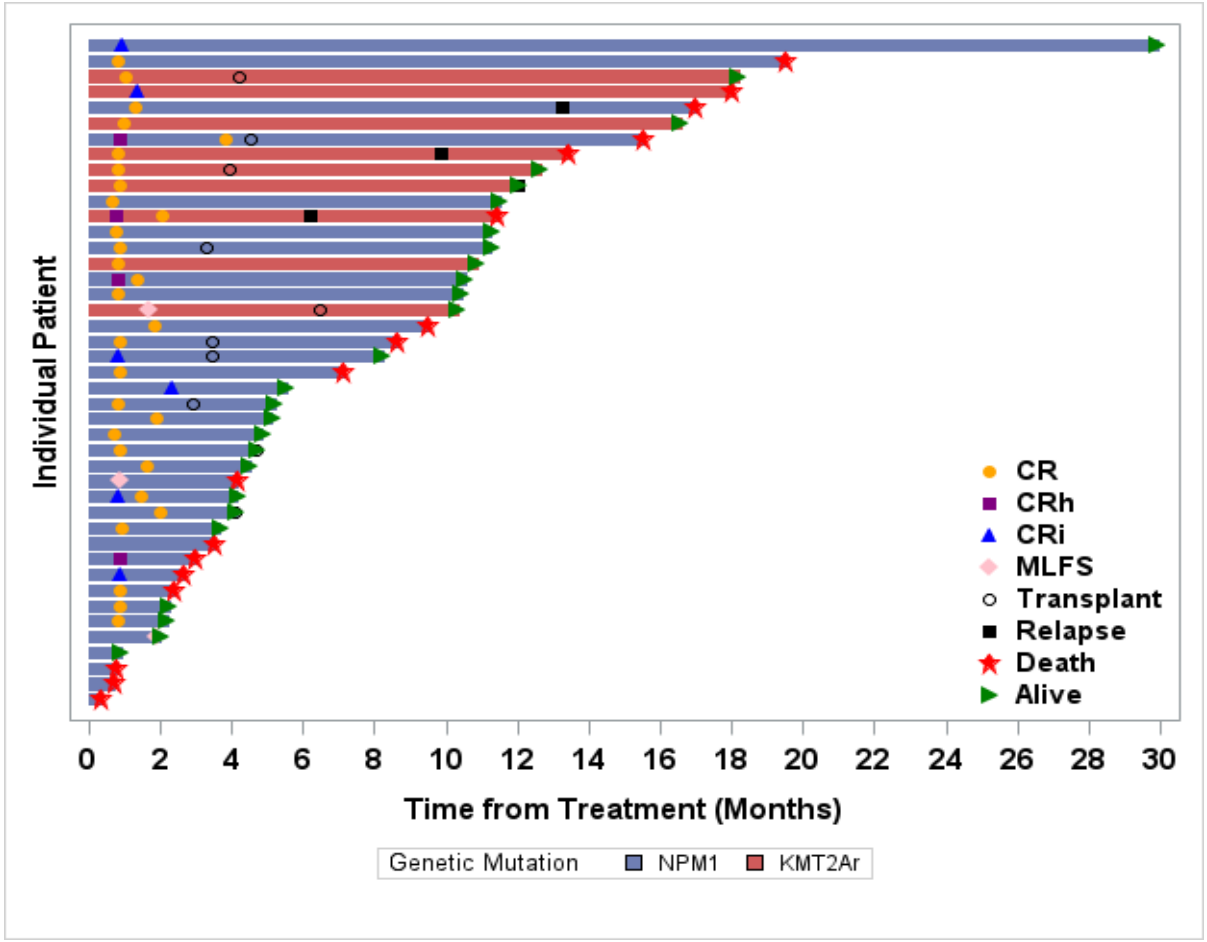
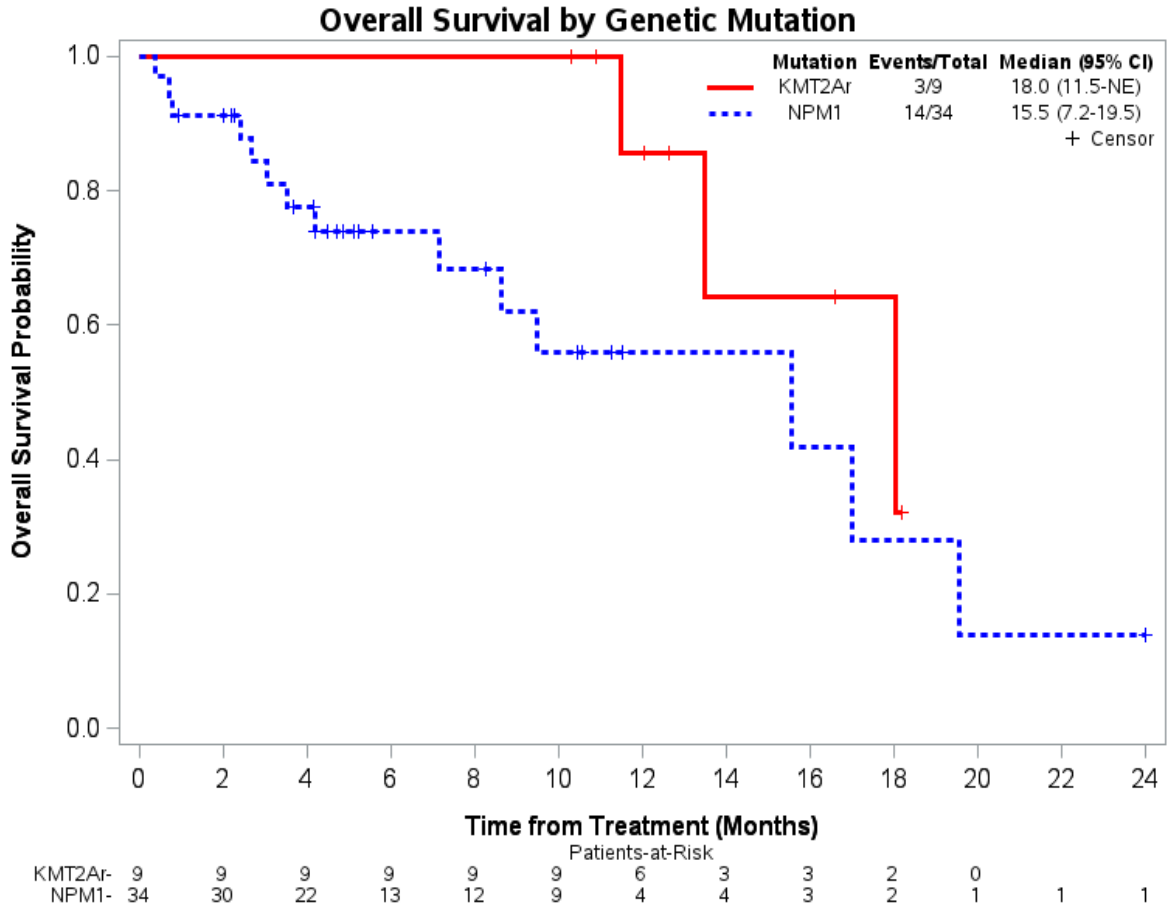
Survival Outcomes of Aza/Ven/Revumenib



- 10 pts (23%) received an allogeneic stem cell transplant
- 4 pts relapsed (*KMT2Ar*: n=3; *NPM1m*: n=1)



- Median F/U = 6.9 months
- 1 year OS = 63% (*KMT2Ar*: 83% vs. *NPM1m*: 55%)

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Conclusions

- 1st clinical trial performed of menin inhibitor + Aza/Ven for newly Dx older/unfit AML patients with *NPM1m* or *KMT2Ar*
- Addition of Revumenib to Aza/Ven safe and feasible at both dose levels in newly Dx older *NPM1m* or *KMT2Ar* AML
- Cytopenias and delays in continuation phase cycles warrant pre-emptive dose reduction of Venetoclax after achievement of remission
  - Study Amended: Ven 14 days every cycle in continuation phase
- Aza/Ven/Revumenib highly active in newly Dx older AML pts w/ *NPM1m* or *KMT2Ar*
  - ORR = 88%, CRc = 81%, CR = 67% with flow MRD-negative remissions seen in all evaluable pts
  - No patient had refractory disease after 1-2 cycles
  - Promising activity in patients with higher-risk disease compare favorably to Aza/Ven
    - *KMT2Ar*: CRc = 89%; *NPM1m* Intermediate-risk: CRc = 79%
- EVOLVE-2[1]: Randomized Phase 3 study currently enrolling: Aza/Ven/Revumenib vs. Aza/Ven/Placebo in newly Dx older/unfit *NPM1m and KMT2Ar* AML

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1- EU CT #2024-512733-32-00; NCT06652438

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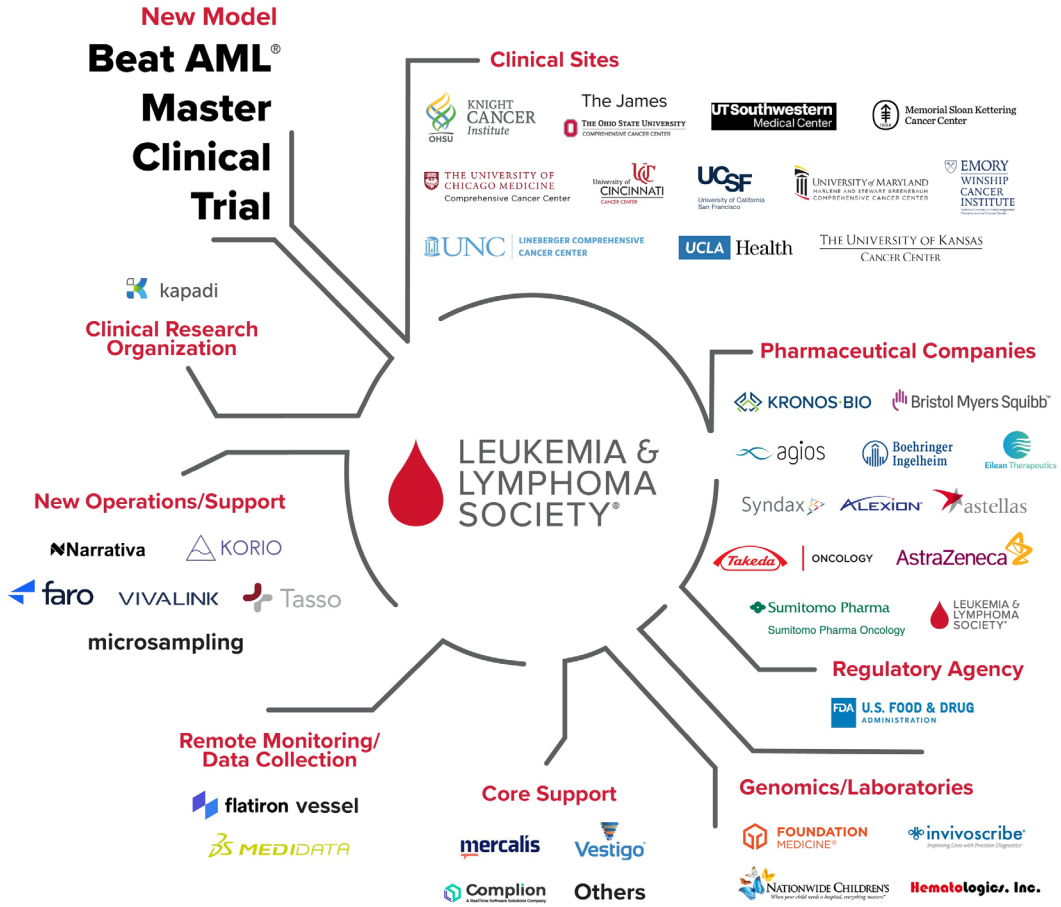

- Patients and families who enrolled on this trial and contributed samples and data
- Clinical research sites for their support and effort.
- Beat AML team for their invaluable support and dedication to the study
- Syndax for their support for this study

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Original Reports | Hematologic Malignancy

Azacitidine, Venetoclax, and Revumenib for Newly Diagnosed *NPM1*-Mutated or *KMT2A*-Rearranged AML

Joshua F. Zeidner, MD[1]; Tara L. Lin, MD[2]; Rina Li Welkie, MPH[3]; Emily Curran, MD[4]; Kristin Koenig, MD[5]; Wendy Stock, MD[6]; Yazan F. Madanat, MD[6]; Ronan Swords, MD, PhD[7]; Maria R. Baer, MD[8]; William Blum, MD[9]; Eytan M. Stein, MD[10]; Rebecca L. Olin, MD, MSc[11]; Gary Schiller, MD[12]; Angela Nichols, MSc[1]; Olatoyosi Odenike, MD[8]; Elie Traer, MD, PhD[1]; Curtis Lachowiez, MD[1]; Vu H. Duong, MD, MSc[4]; Michael J. Hochman, MD[8]; Sheng F. Cai, MD, PhD[13]; Catherine Smith, MD[11]; Mona Stefanos, MBChB[8]; Molly Martycz, MSc[8]; Ying Huang, MSc[8]; Len Rosenberg, PhD[13]; Sonja Marcus, MPH[13]; Timothy L. Chen, PhD[3]; Ashley O. Yocum, PhD[13]; Brian J. Druker, MD[1]; Ross L. Levine, MD[13]; Uma Borate, MBBS[1]; John C. Byrd, MD[4]; and Alice S. Mims, MD[1]

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ABSTRACT

PURPOSE Azacitidine and venetoclax is a standard frontline treatment regimen for newly diagnosed older adults with AML; however, long-term outcomes remain poor. Revumenib is an oral menin inhibitor with clinical activity in AML patients with nucleophosmin-1 mutation (*NPM1m*) or lysine methyltransferase 2A rearrangements (*KMT2Ar*).

METHODS We conducted a phase I dose-escalation and expansion study of azacitidine, venetoclax, and revumenib at two dose levels (113 mg or 163 mg orally every 12 hours in combination with strong cytochrome P450 inhibitor azoles) in patients aged 60 years and older newly diagnosed with AML with *NPM1m* or *KMT2Ar* (ClinicalTrials.gov identifier: NCT03013998).

RESULTS Overall, 43 patients were enrolled and treated. There was no maximal tolerated dose identified. Differentiation syndrome was present in eight (19%) patients and QTcF prolongation was present in 19 (44%) patients, and neither required permanent discontinuation of revumenib. The overall response rate with an intention-to-treat population was 88.4% (95% CI, 74.9 to 96.1; *NPM1m*: 85.3%; *KMT2Ar*: 100%), the rate of composite complete remission (CR; CR + CR with partial or incomplete hematologic recovery) was 81.4% (95% CI, 66.6 to 91.6; NPM1m: 79.4%; KMT2Ar: 88.9%), and the rate of CR was 67.4% (95% CI, 51.5 to 80.9; *NPM1m*: 65%; *KMT2Ar*: 78%). No patient had refractory disease after 1-2 cycles of treatment. The median time to first response was 28 days, and 84% of responders achieved remission within the first cycle. All 37 patients evaluated had no evidence of measurable residual disease by a centralized flow cytometry assay.

CONCLUSION In older adults newly diagnosed with *NPM1m* or *KMT2Ar* AML, the combination of azacitidine, venetoclax, and revumenib was able to be safely administered with high rates of CR and clinical activity.

ACCOMPANYING CONTENT

- Appendix
- Data Sharing Statement
- Data Supplement
- Protocol

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INTRODUCTION

AML is an aggressive myeloid malignancy that predominantly affects older adults with a median age of 68-70 years. Historically, AML outcomes have been poor, particularly in older adults, with 5-year overall survival (OS) rates <10% in patients aged 65 years and older.[1] Owing to older age and/or comorbidities, a large proportion of patients with AML are unfit and ineligible to receive intensive chemotherapy. The combination of azacitidine and the B-cell lymphoma 2 antagonist venetoclax was shown to significantly improve complete remission (CR) rates (36.7% *v* 17.9%) and median OS (14.7 *v* 9.6 months) compared with azacitidine and placebo in patients with newly diagnosed AML unfit for intensive chemotherapy and/or aged 75 years and older, leading to a new standard of care for this patient population.[2] However, long-term outcomes remain poor with 2-year OS rates <40%.[3]

Nucleophosmin-1 mutations (*NPM1m*) and lysine methyltransferase 2A rearrangements (*KMT2Ar*) are AML-defining genetic abnormalities seen in approximately 30% and 5% of all patients with AML, respectively, and share similar gene expression profiles with aberrant menin-dependent

Azacitidine, Venetoclax, and Revumenib for Newly Diagnosed NPM1-Mutated or KMT2A-Rearranged AML

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